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Smell and Taste Symptom-Based Predictive Model for COVID-19 Diagnosis

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Abstract

Background: The presentation of COVID-19 overlaps with common influenza symptoms. There is limited data on whether a specific symptom or collection of symptoms may be useful to predict test positivity.

Methods: An anonymous electronic survey was publicized through social media to query participants with COVID-19 testing. Respondents were questioned regarding 10 presenting symptoms, demographic information, comorbidities and COVID-19 test results. Stepwise logistic regression was used to identify predictors for COVID positivity. Selected classifiers were assessed for prediction performance using receiver operating characteristic analysis (ROC).

Results: One-hundred and forty-five participants with positive COVID-19 testing and 157 with negative results were included. Participants had a mean age of 39 years, and 214 (72%) were female. Smell or taste change, fever, and body ache were associated with COVID-19 positivity, and shortness of breath and sore throat were associated with a negative test result ($p<0.05$). A model using all 5 diagnostic symptoms had the highest accuracy with a predictive ability of 82% in discriminating between COVID-19 results. To maximize sensitivity and maintain fair diagnostic accuracy, a combination of 2 symptoms, change in sense of smell or taste and fever was found to have a sensitivity of 70% and overall discrimination accuracy of 75%.

Conclusion: Smell or taste change is a strong predictor for a COVID-19 positive test result. Using the presence of smell or taste change with fever, this parsimonious classifier correctly predicts 75% of COVID-19 test results. A larger cohort of respondents will be necessary to refine classifier performance.

Introduction

In mid-January 2020, the World Health Organization (WHO) reported 41 cases of a novel coronavirus infection that presented with fever, shortness of breath (SOB), and invasive pneumonic infiltrates on chest radiography.[1] Since that initial report, this novel coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally, with confirmed cases in almost every country.[2]

With the swift spread of cases resulting in the virus' diseased state known as COVID-19, development of reliable assessment methodologies to accurately predict and diagnose COVID-19 infection is paramount to controlling its spread. Currently, the availability of COVID-19 testing remains a limited resource. Insufficient access to testing supplies and reagents highlights the need to selectively restrict test kit usage to a relatively limited number of individuals. Many patients, including healthcare workers, are not tested as they do not meet "testing criteria" due to lack of an identifiable positive contact, lack of travel to a highly infected area or lack of the common screening symptoms.

While publicized symptoms for COVID-19 include fever, fatigue, cough and shortness of breath,[3,4] several studies have also reported chemosensory dysfunction, such as anosmia and ageusia as common findings in COVID positive patients.[5-7] Although upper respiratory infections are known to cause hyposmia in general,[8] in COVID-19 patients, these symptoms can present in the absence of other nasal symptoms, suggesting that they are related to direct viral damage to

the chemosensory system.[5,9] Within the United States, a study of COVID-19 tested subjects revealed a significant association of smell and taste impairment in COVID-19 positive patients.[10] A survey study of 417 European COVID-19 patients identified cough, myalgia and loss of appetite as the most common general presenting symptoms, with a significant percentage (86%) of patients noting smell dysfunction.[11] Based on these reports, it appears that smell and taste changes may be significant findings to consider when screening for COVID-19 infection.[12]

Several studies have developed prediction models for COVID-19, most of which have focused on prognostic factors for survival.[13] A few prediction models for diagnosis have been published, but have mostly identified chest computed tomography (CT) and other laboratory findings as predictors.[14] One COVID-19 diagnostic model identified the following key symptoms: fever, fatigue, shortness of breath, headache and sore throat.[15] Smell and taste change have not been evaluated in any prediction models to date. We sought to address this information gap and included smell and taste change to construct prediction models for COVID-19 positivity. We aimed to identify a parsimonious subset of symptoms that would enable a clinically tractable classifier to predict COVID-19 positivity to improve both decision making on test resource allocation and evidence-based counseling of concerned patients.

Methods

The study was reviewed by the University of California, San Francisco (UCSF) Institutional Review Board and was given exempt status (IRB# 20-30530). With the objective of obtaining a large number of responses over a short time period during this highly critical time of data collection and dissemination, an anonymous survey was publicized through several social media outlets. The public survey link was posted on social media venues including Facebook, Twitter, Reddit, and Nextdoor targeting participant volunteers who had been tested or quarantined for COVID-19 symptoms. Anonymous, self-reported responses were collected

between March 31, 2020 and April 10, 2020. Groups of healthcare workers treating COVID-19 patients were also targeted. Recruitment included participants who identified as older than 18 years and had a history of prior COVID-19 testing or history of being quarantined for symptoms of COVID-19. To avoid bias, the survey title, "UCSF COVID-19 Symptom Survey," and questions, focused on broad COVID-19 symptoms and presentation. Respondents reported COVID-19 test results, demographic information and COVID-19 related comorbidities. The survey included forced choice, binary (yes/no) questions about the presence of 10 symptoms in the 2 weeks leading up to their test or quarantine: change in smell or taste, fever or chills, unexplained body aches, new sore throat, shortness of breath, new headache, new or worsened cough, nasal congestion, nausea or diarrhea, and runny nose.

Database Management and Statistical Analysis

Data were collected and managed using Research Electronic Data Capture tools hosted at UCSF (REDCap Consortium, Vanderbilt University, Nashville, TN), and Microsoft Excel (Microsoft Corp, Redmond, WA).

Statistical analysis was preformed using Statistical Package for the Social Sciences version 26 (SPSS, IBM Corp., Armonk, NY). Demographic information was reported using descriptive statistics and univariate analysis was used to evaluate the incidence of each presenting symptom. Using the self-reported COVID-19 positive result, analysis was performed for each individual significant symptom to determine sensitivity = [true positives / (true positives + false negatives)] and specificity = [true negatives / (true negatives + false positives)]. Stepwise, forward selection, binary logistic regression was performed with COVID-19 test result as the dependent variable and presence or absence of each classic COVID-19 symptom, gender, number of comorbidities, age and presence of chronic lung disease as independent variables to determine significant predictors for COVID-19 positivity. The stepwise regression included

thresholds of p=0.05 for entry and 0.10 for removal with maximum iterations set at 20 and classifier cutoff at 0.5. This analysis was used to determine the best predictors for COVID-19 positive test results. To assess for potential effects of all symptoms and confounders, all 14 variables were also entered in a full logistic regression model. Fourteen potential predictor variables were assessed for our cohort of 145 COVID positive subjects, which met the goal events per candidate predictor of 10 (Hosmer and Lemeneshow rule) to avoid model overfitting.[16]

Internal validation of the predictors identified was performed using a randomly generated sample of 75% of the cohort (development set). This cohort was used to create a stepwise logistic regression model that was tested on the remaining 25% of the cohort (validation set), and classifier performance was examined. Cases without missing information (n=246) were used for internal validation.

Receiver operating characteristic (ROC) curves were created to assess predictor performance after selecting relevant symptom classifiers based on the regression model and clinical utility. Area under the curve (AUC) analysis was performed to assess the ability of symptom classifiers to discriminate COVID positive subjects from COVID negative subjects. Statistical significance was set at p-value less than 0.05 for all analyses.

Results

Study Participants

Six hundred and twenty participants enrolled in the study between March 31, 2020 and April 10, 2020. Three hundred and thirty-nine participants reported a prior COVID-19 test, 145 subjects (43%) had a positive test result (COVID+), 157 subjects (46%) reported a negative test result (COVID-), and 37 (11%) reported no result or uncertain result. Participants who reported a positive or negative test result (n=302) at the time of the survey were included in

this analysis. The cohort was predominantly female with a higher proportion of females in the COVID negative group (Table 1). Eleven (4%) respondents had been hospitalized (8 COVID+ and 3 COVID-, p =0.095). There were no differences in age, race or ethnicity between positive and negative COVID-19 test groups. A higher percentage of COVID–19 negative patients reported chronic lung disease from asthma, COPD, or emphysema as compared to COVID–19 positive participants ($\chi^2(1, N = 302) = 5.69$, $p = 0.017$).

Symptom Presentation

Based on self-reporting of the 2 weeks prior to undergoing COVID-19 testing or initiating quarantine for symptoms, the presence of fever, smell or taste change and body aches were significantly associated with a positive diagnosis of COVID-19, whereas shortness of breath and sore throat were associated with a negative COVID-19 test result (Table 2). Incidence, sensitivity and specificity of each symptom queried for COVID-19 test result discrimination are shown in Table 2. Unexplained body aches demonstrated the highest sensitivity (80%) in univariate analysis, while change in smell or taste had the highest specificity (73%). Only one participant with a positive COVID test result reported none of the 10 symptoms.

Determining Predictors of COVID-19

Stepwise, forward selection, binary logistic regression analysis was performed to determine the predictor variables associated with a COVID positive test result. The five classifier variables identified as the best predictors included the presence of smell or taste change, unexplained body aches, fever or chills, shortness of breath, and sore throat. Variables that fell out of the stepwise regression model, and were not significant in the analysis, included age, gender, history of lung disease, number of comorbidities, and presence of cough,

rhinorrhea, nasal congestion, headache, or nausea or diarrhea. Each step in the model was statistically significant ($p < 0.005$), the final model (step 5) accounted for 44% of the variability of the outcome (Nagelkerke $R^2 = 0.44$) and the Hosmer and Lemeshow test demonstrated $p>0.05$ for all model steps denoting good model fit. Smell or taste change was the strongest predictor identified and when used as a sole classifier, accounted for 24% of the variability in the COVID positive test outcome (Nagelkerke $R^2 = 0.24$). Table 3 shows the logistic regression coefficient, Wald test, and odds ratio for each of the predictor variables and models. Fever or chills, smell or taste change, and myalgia were positively associated with a COVID positive test. Based on the step 5 predictor model created, the odds ratio for smell or taste change shows that when holding all other variables constant, an individual who reports smell or taste change is 7.4 times more likely to have a COVID positive test than one who does not report smell or taste change. Although significant, the effect of fever and myalgia was smaller than the effect from smell or taste change. An individual who reports fever is 2.4 times, and a person with myalgia is 3.1 times more likely to have a COVID positive test. Reported shortness of breath and sore throat were associated with a COVID negative result. Inverted odds ratios indicate that the odds of COVID negative result were 5 times higher if shortness of breath was reported and 3.3 times higher if sore throat was reported (Table 3). Full binary logistic regression with all 14 variables was done to evaluate the effect of all symptoms and potential confounders. The analysis identified the same 5 symptom variables as significant predictors and the other variables were not significant. Smell or taste change was associated with the largest odds ratio for COVID-19 positivity. Adjusted odds ratios were similar to the final model in the stepwise logistic regression (Supplemental table 1).

Classifier Performance and Discrimination

The selected predictors from the regression model were internally validated by splitting the cohort into a random 75% set (n =184) for classifier development and a 25% (n=62) set,

which was used for validation. Stepwise logistic regression performed on the development set produced the same 5 predictors as when the analysis was run on the entire cohort. Table 4 shows the performance of the predictor model on the development and validation cohorts. Accuracy is defined as the sum of true positive and true negative cases relative to the total number of cases. The final predictor model created was able to correctly classify 74% of COVID positive test results and 71% of COVID negative results for an overall accuracy of 73% for the validation set. Accuracy of the validation set was within 3.5% of the development set.

Using classifiers identified from the regression model and clinical judgment, we chose to evaluate classifier discrimination for smell or taste change alone and with the presence of fever, myalgia, fever and myalgia, or absence of sore throat. To assess the discrimination ability of symptom predictor combinations, sensitivity and specificity analysis were performed and ROC curves were plotted. AUC analysis to measure classifier performance using the presence of smell or taste change with either fever and/or myalgia showed fair diagnostic accuracy (AUC=0.75, Table 5) with 75% correct discrimination of COVID positivity. Very good classifier performance (AUC = 0.82) required the inclusion of all 5 statistically modeled predictors (change in smell or taste, fever, myalgia, sore throat and shortness of breath).[17]

Discussion

In this study, we aimed to assess the symptoms associated with a COVID-19 positive test in an outpatient population of individuals who were suitably healthy to complete the survey. While we included smell and taste questions in our survey, we recruited any participant with a COVID-19 test result regardless of specific symptoms. The goal of determining symptom-based predictors for COVID-19 was to better define those at risk for COVID-19 infection for test resource allocation and patient counseling. Through logistic regression, we have identified and

assessed the ability of symptom sets to accurately classify subjects as COVID–19 positive. Symptoms associated with COVID-19 positivity included the change to smell or taste, presence of fever and body aches, and absence of shortness of breath and sore throat. While our findings differ from a European study that identified cough and GI symptoms as common in COVID-19,[11] our results are similar to other published work which reported both loss of smell and absence of sore throat in COVID-19 positive patients with an adjusted odds ratio of 10.9 for COVID-19 positivity if anosmia was reported.[10] We have similarly identified smell or taste change as the symptom with the strongest correlation to a COVID + result, accounting for 24% of the variance in COVID test results. Variation most likely relates to differences in geographic locale and sample cohort COVID-19 severity.

When screening patients for COVID-19 positivity during this pandemic, is it important to consider both data driven information and reasoned clinical judgment. The statistical model using 5 diagnostic variables showed the highest overall accuracy of 82%, but the sensitivity of this model was low at 56%. Given the importance of a screening protocol with high sensitivity and exercising clinical judgment responsive to an evolving pandemic, we chose to assess performance of classifiers with the following symptoms: 1) presence of smell or taste change and fever and 2) presence of smell or taste change and myalgia. Both prediction models performed very well with sensitivities between 69-70%, specificity of 73%, and overall discrimination accuracy of 74-75%. The diagnostic accuracy of adding either fever or myalgia to smell or taste change was minimal. We believe that either of these models are clinically reasonable when considering COVID-19 patients, and both also performed well statistically.

Based on the favorable general health status of our outpatient study cohort constituted by younger adults with relatively few comorbidities and reasoned clinical judgment of symptom progression in severe COVID-19 infection, we chose to exclude absence of shortness of breath in prediction model performance analysis. As shortness of breath was found to be negatively associated with COVID-19 positivity in the statistical model, we reported the association. We do

not recommend inclusion of shortness of breath as a negative predictor of disease because it is a marker of more severe COVID-19 disease that may not have been captured in the surveyed cohort. Chronic lung disease was found to be more common in COVID-19 negative participants in this analysis and may be related to patients with lung disease seeking testing and medical treatment more frequently than their healthy counterparts. Moreover, our data suggest that a higher proportion of males were COVID-19 positive, but we cannot exclude selection bias in seeking testing or in participating in an online survey.

Limitations of this study include dependence on retrospective self-reporting with risk of recall bias regarding symptoms, possible duplicate entries, and selection bias of respondents to an anonymous online survey posted on social media. Due to the anonymous nature of this study and wide circulation to participants across the country, respondents were asked to self-report their COVID-19 results leading to potential erroneous responses. Additionally, COVID-19 test performance indices are variable across testing locations, and specifics regarding testing procedures were not assessed, possibly contributing to variance in prediction model performance. While we are not able to review patient medical records in this study, model validation results confirm that drawing from a large and diverse pool of subjects mitigates risk of self-report errors from degrading prediction models in a significant manner. Lastly, we acknowledge that patient symptoms may change over time during the duration of their illness and asymptomatic and atypical presentations of COVID–19 have been reported.[18,19] Therefore, while our models will be helpful for identification of at-risk patients, it is important to remain vigilant for less common presenting symptoms of COVID–19.

Online tools are under development for individual risk assessment of infection, and data to support these risk calculations will be extremely useful. The cohort evaluated in this study was relatively healthy, and able to participate in an online study. The survey responses may not reflect diverse populations of the United States, as age and race were not significant factors in our analysis. While our work is exploratory, it represents one of the first steps to construct

accurate predictor models for COVID-19 positivity. Further work should include hospitalized patients to develop a more comprehensive prediction model that may be deployed broadly across the United States and abroad. More robust methods for prediction model development will require larger data sets and cross-validation studies.

Conclusion

Chemosensory function change is strongly associated with a COVID-19 positive test. In an outpatient population with few comorbidities, combining symptoms of smell or taste change with fever and/or myalgia predicts COVID-19 positivity with fair accuracy. We believe that this information is highly valuable at a time in which testing resources remain highly constrained and important decisions must be made regarding testing resource allocation. While not a surrogate for testing, using predictive symptoms to determine pre-test probability for COVID-19 positivity can inform next steps in clinical decision-making under uncertain circumstances.

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Figure Legend

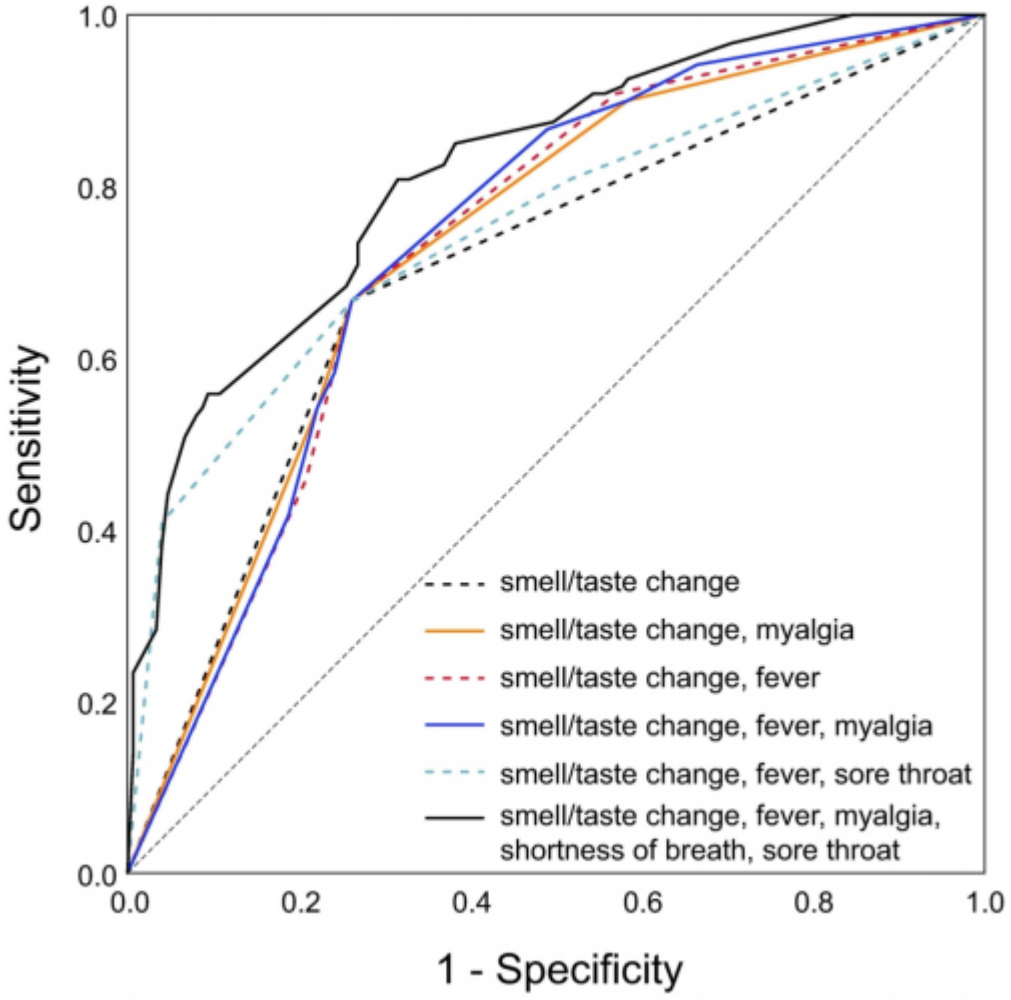

Figure 1. Receiver operating characteristic (ROC) plots for symptom classifier models. The dashed diagonal line shows a non-diagnostic result. Area under the curve (AUC) for each symptom classifier group is displayed in Table 5.

TABLE 1. Demographic Information

	COVID +	COVID -	χ^2 or F	p-value
Total n (%)	145 (48%)	157 (52%)		
Age, years mean (SD)	40 (13)	38 (11)	8.32	0.33
Sex, female n (%)	94 (65%)	120 (78%)	6.37	0.01*
Number of Comorbidities n (%)			5.05	0.17
0	120 (83%)	113 (72%)		
1	20 (14%)	36 (23%)		
2	4 (3%)	6 (4%)		
≥3	1 (0.7%)	2 (1%)		
Presence of chronic lung disease n (%)	13 (9%)	29 (18%)	5.70	0.02*

SD = standard deviation, *p<0.05 denotes significance

COVID + = COVID-19 positive test; COVID - = COVID-19 negative test

TABLE 2. Symptom Features

	COVID +	COVID-	Sensitivity	Specificity	p-value
	n (%)	n (%)	[95% CI]	[95% CI]	
Unexplained body aches	112 (77%)	87 (55%)	80% [72% – 86%]	44% [36% - 52%]	< 0.001
Fever or chills	106 (73%)	82 (52%)	73% [65% – 80%]	47% [39% - 56%]	< 0.001
Change in smell or taste	95 (66%)	42 (27%)	70% [61% - 77%]	73% [65% - 80%]	< 0.001
New sore throat	59 (41%)	107 (68%)	70% [62% - 77%]	54% [44% - 63%]	< 0.001
Shortness of breath	50 (34%)	81 (52%)	53% [45% - 61%]	62% [53% - 70%]	0.009
New headache	93 (64%)	90 (57%)			0.085
New or worsened cough	79 (54%)	104 (66%)			0.070
Nasal congestion	68 (47%)	61 (39%)			0.082
Nausea or diarrhea	64 (44%)	62 (39%)			0.347
Rhinorrhea	52 (36%)	54 (34%)			0.652

CI = Confidence Interval; p<0.05 denotes significance
COVID + = COVID-19 positive test; COVID - = COVID-19 negative test

TABLE 3. Stepwise Logistic Regression, Predictors for COVID Positive Test Result

	Predictor(s)	B	Wald	p-value	Odds Ratio [95% CI]
Step 1	Smell or taste change	1.92	44.2	<0.001	6.8 [3.9-12.0]
Step 2	Smell or taste change	2.27	47.4	<0.001	9.7 [5.1-18.5]
	Shortness of breath	-1.30	15.2	<0.001	0.3 [0.1-0.5]
Step 3	Smell or taste change	2.22	43.0	<0.001	9.2 [4.7 - 17.8]
	Shortness of breath	-1.69	21.4	<0.001	0.2 [0.1-0.4]
	Fever or chills	1.20	12.8	<0.001	3.3 [1.7-6.4]
Step 4	Smell or taste change	2.17	39.4	<0.001	8.7 [4.4-17.2]
	Shortness of breath	-1.58	18.0	<0.001	0.2 [0.1-0.4]
	Fever or chills	1.29	12.8	<0.001	3.6 [1.8-7.1]
	New sore throat	-0.97	9.1	0.003	0.4 [0.2-0.7]
Step 5	Smell or taste change	2.01	32.6	<0.001	7.4 [3.7-14.8]
	Shortness of breath	-1.74	20.2	<0.001	0.2 [0.1-0.4]
	Fever or chills	0.87	5.3	0.021	2.4 [1.1-5.0]
	New sore throat	-1.16	11.6	0.001	0.3 [0.2-0.6]
	Body aches	1.14	7.9	0.005	3.1 [1.4-7.0]

Variable(s) entered on:

Step 1: Smell or taste change
Step 2: Shortness of breath

Step 3: Fever or chills

Step 4: New sore throat

Step 5: Body aches

TABLE 4. Classifier Validation

		Development Set (n=184)			**Validation Set** (n=62)		
	Predictors	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Step 5	Smell or taste change	77.9	74.5	76.1	74.1	71.4	72.6
	Shortness of breath						
	Fever or chills						
	New sore throat						
	Body aches						
Accuracy = (True positive cases + True negative cases)/Total number of cases							

TABLE 5. Classifier Performance

Predictor Set	AUC	Sensitivity	Specificity	Odds Ratio [95% CI]	p-value
Smell or taste change	0.71	70	73	6.18 [3.71-10.29]	<0.001
Smell or taste change Myalgia	0.74	69	73	6.20 [3.71-10.33]	<0.001
Smell or taste change Fever	0.75	70	73	6.33 [3.79-10.56]	<0.001
Smell or taste change Myalgia Fever	0.75	69	74	6.35 [3.79-10.63]	<0.001
Smell or taste change Sore throat	0.75	67	74	5.74 [3.41-9.69]	<0.001
Smell or taste change Myalgia Fever Sore throat Shortness of breath	0.82	56	89	8.93 [5.59-19.76]	<0.001

AUC = Area under the curve, CI = Confidence Interval, p-value<0.05 denotes significance						